Supporting Information

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SI Methods

Fluorophore Labeling of Fibrils. Fibrils of β_2m labeled with 5-(and 6)-carboxytetramethylrhodamine-succinimidyl ester (TMR) (Invitrogen-Molecular Probes) were prepared from labeled β_2m monomers mixed 1:9 with unlabeled wild-type monomers and seeded with 0.1% (wt/wt) fragmented fibrils. To label the monomers, a 10-fold molar excess of TMR over β_2m was used. TMR was dissolved in DMSO at a concentration of 1 mg/mL and added dropwise to a stirring β_2m solution (10 mg/mL in $Na_2{\cdot}HCO_3$) in the dark for 1 h. A PD10 desalting column (Amersham Biosciences) was equilibrated using 25 mL of 100 mM Tris·HCl pH 8.0. Subsequently, 2.5 mL of the TMR-β_2m conjugate was loaded onto the column and eluted using 3.5 mL of 100 mM Tris·HCl, pH 8.0. The TMR-β_2m conjugate was dialyzed against water, lyophilized, and stored at –20 °C. Monomer was labeled with two, three, four, or five TMR molecules per monomer with a ratio of ~1:2:2:1 as determined by electrospray ionization mass spectrometry.

Extrusion of LUVs. A 20 μL aliquot of the chloroform solution of 4:1 PC–PG was dried under a stream of nitrogen for at least 30 min and then under vacuum for at least 1 h, and then resuspended by vortexing for 5 min in 50 mM Hepes, 107 mM NaCl, 1 mM EDTA, pH 7.4 (liposome buffer) to final concentrations of 1.3, 2.6, or 3.9 mM lipids. This suspension was then sonicated for 20 s in an ultrasound bath to remove excess air and foam and then extruded (Avanti Lipids Mini-Extruder) through polycarbonate filters with 100 nm pore size 25 or 30 times. Liposomes were stored at room temperature and used within 24 h of preparation.

Rapid Evaporation to Produce Giant Vesicles. A total of 500 μL of aqueous phase containing the liposome buffer supplemented with 0.1 M sucrose was added to 200 μL of the fluorescently labeled lipid solution in chloroform to a round-bottom flask, followed by brief vigorous mixing of the two phases by pipetting. The organic solvent was immediately removed in a rotary evaporator under reduced pressure (final pressure 40 mbar) for 2–3 min at room temperature. The resulting vesicle suspension exhibited a slightly turbid appearance and was used on the day of preparation. The final lipid concentration was 2 mM. Similar results were obtained with 4:1 mixtures and 1:1 mixtures of PC–PG (compare Fig. 2 with Figs. S3*A* and S4*A*).

Time Course of Fluorescence Measurements. To acquire confocal images, giant vesicles must be deposited from solution onto a glass slide, which takes 5–15 min. When monitoring interaction of GVs with a small, soluble protein or protein oligomers, the protein can be applied without disturbing the layer of vesicles, diffusion enabling the mixing of the sample (1). By contrast amyloid fibrils have a low diffusion rate so that the samples must be mixed with the vesicles before deposition onto the glass slide. Thus, images cannot be obtained until at least 5 min after initiating the reaction. From this time point, time-lapse imaging failed to reveal any additional morphological changes of the vesicles or fibrils, as their interaction is faster than the experimental setup.

1. Beales PA, Bergstrom CL, Geerts N, Groves JT, Vanderlick TK (2011) Single vesicle observations of the cardiolipin-cytochrome C interaction: Induction of membrane morphology changes. *Langmuir* 27(10):6107–6115.

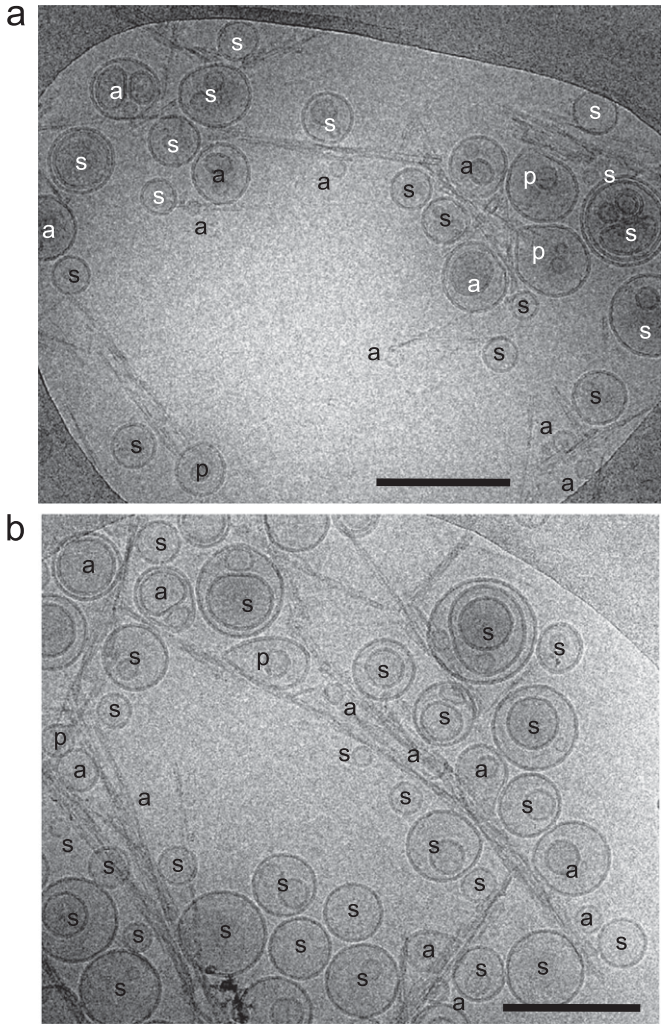


Fig. S1. Example areas showing classification of liposomes into pointed (P), smoothly rounded (S), or ambiguous (A). The ambiguous category is for liposomes that are obscured by contacts with fibril bundles and/or other liposomes, precluding their reliable identification as either pointed or smooth. (*A*) Liposomes incubated with short β_2m fibrils; (*B*) liposomes incubated with long β_2m fibrils. (Scale bar: 200 nm.)

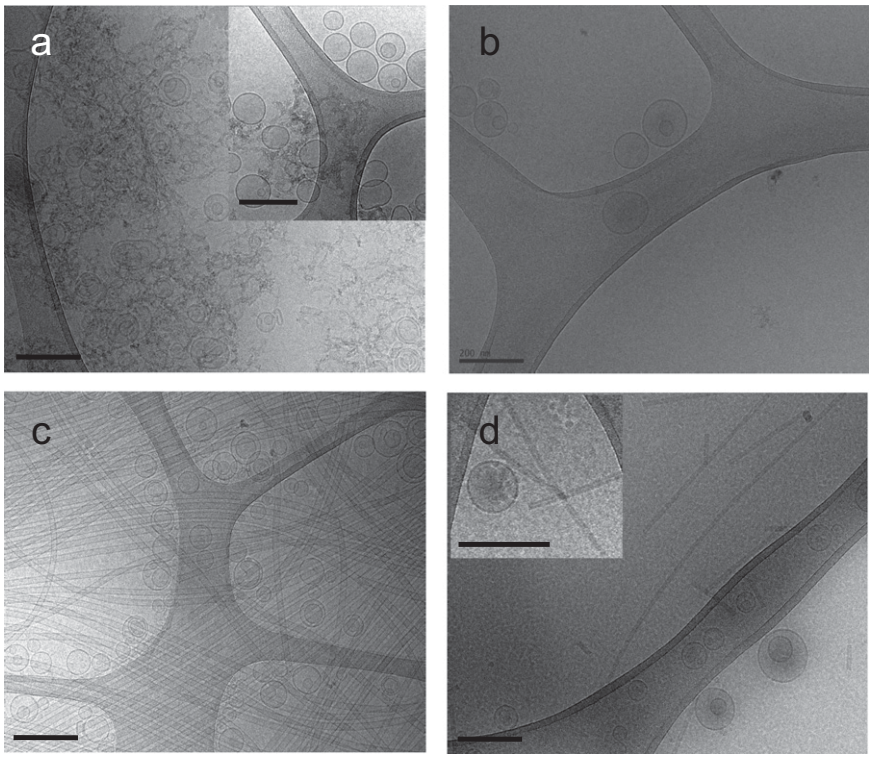


Fig. S2. Cryo-EM images of control samples with PC–PG liposomes, showing lack of distortion and weak or absent interactions. (*A*) WL β_2m fibrils with PC–PG liposomes. This sample also contained areas of free liposomes on other parts of the grid, one of which is shown in the inset. (*B*) Liposomes in the presence of β_2m monomers (19 μM monomer, equivalent to the subunit concentration in the fibril samples). (*C*) Microtubules with liposomes. (*D*) TMV filaments with liposomes. The inset shows a liposome near the end of a TMV filament. (Scale bar: 200 nm.) Note that liposomes alone are blotted off during grid preparation, but more are retained if they are bound by fibrils.

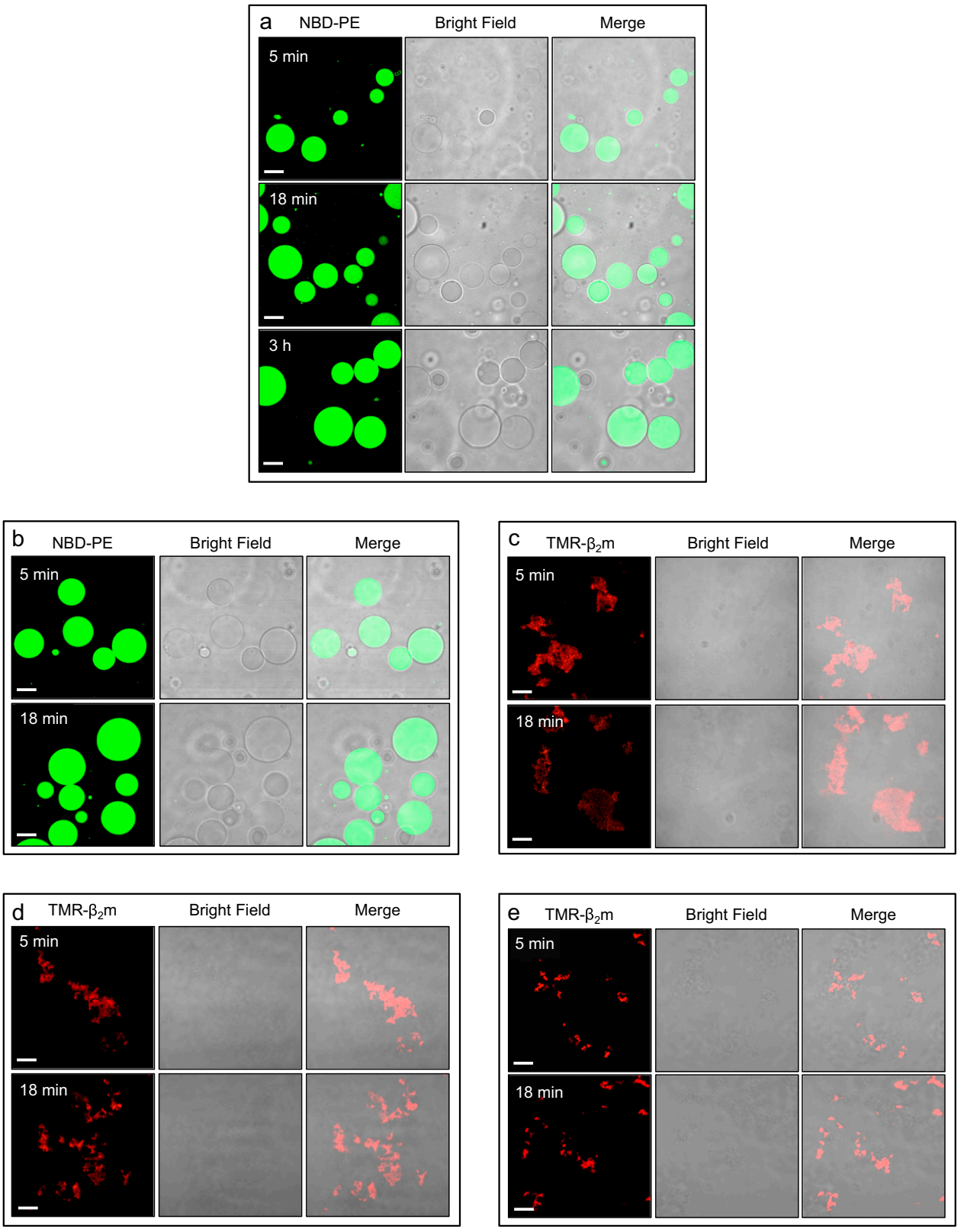


Fig. S3. Fluorescence microscopy of control samples. (*A*) Liposomes alone, (*B*) liposomes incubated with TMR-labeled β_2m monomer, (*C*) short β_2m fibrils alone, (*D*) long β_2m fibrils alone, and (*E*) WL β_2m fibrils alone. All measurements were performed in liposome buffer at pH 7.4. The images were obtained following incubation times of 5 min, 18 min, or 3 h. Green, NBD-PE labeled giant vesicles; red, TMR-labeled β_2m fibrils. (Scale bar: 20 μm.) TMR-labeled β_2m monomers alone or with liposomes do not give rise to detectable fluorescence under the conditions of these experiments. Note that liposomes alone (*A*) or liposomes incubated with β_2m monomer (*B*) remain stable with no evidence of lipid extraction over the entire time course.

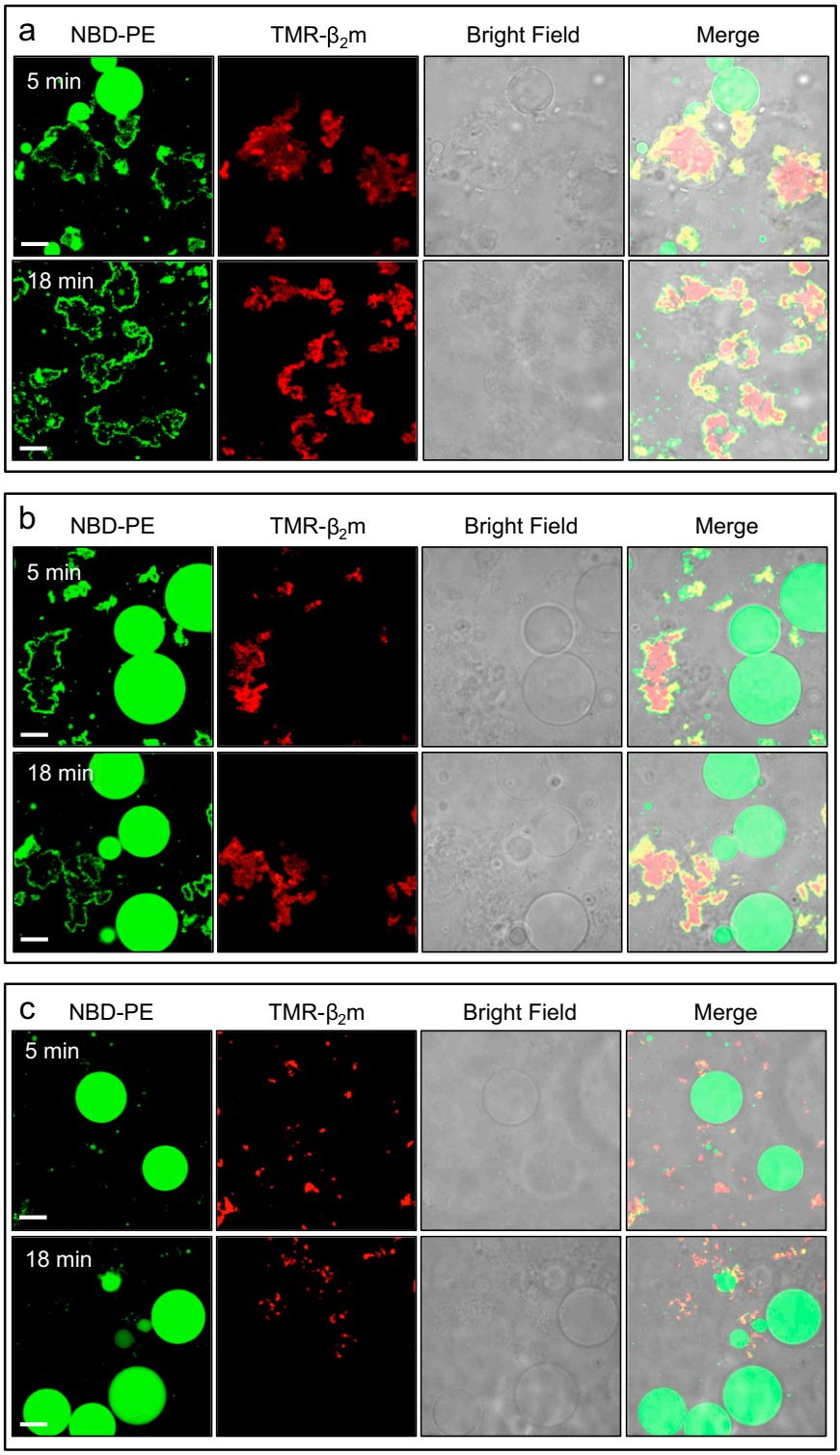


Fig. S4. Fluorescence microscopy showing different types of β_2m fibrils incubated with giant vesicles. (*A*) Liposomes incubated with short β_2m fibrils, (*B*) liposomes with incubated long β_2m fibrils, and (*C*) liposomes incubated with WL β_2m fibrils. The images were obtained after incubation times of 5 or 18 min. Green, NBD-PE labeled giant vesicles; red, TMR-β_2m fibrils. (Scale bar: 20 μm.) Colocalization of lipids and fibrils is indicated by yellow.

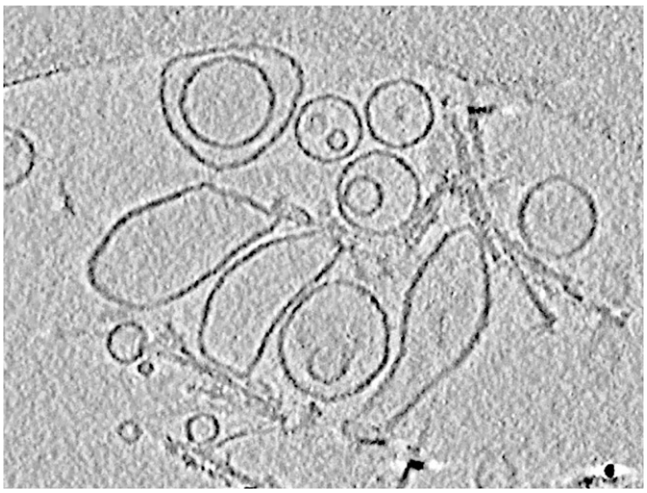
Table S1. Counting statistics of liposome distortions caused by short and long fibrils

	Short fibrils			Long fibrils		
Distortion	Pointed	Smooth	Ambiguous*	Pointed	Smooth	Ambiguous*
Weighted average %[†]	5.3 ± 1.5	42.2 ± 5.2	52.5 ± 5.5	0.9 ± 0.1	65.0 ± 8.8	34.3 ± 1.9
R[‡]		0.126			0.014	
Total counts		2,900			2,554	

The fraction of distorted liposomes counted in EM images is lower than that suggested by the fluorescence image shown in Fig S4*A*. Because these experiments are on very different scales, the measurements are not quantitatively comparable.

*Liposomes that are partially obscured by contacts within the aggregates so that they cannot be reliably classified as either pointed or smooth. We adopted a very conservative approach in which the criterion for assigning liposomes in the pointed category was more stringent for the short fibril sample than for the long; that is, we erred on the side of underestimating the number of pointed liposomes in the short fibril samples and overestimating pointed liposomes in the long fibril samples.

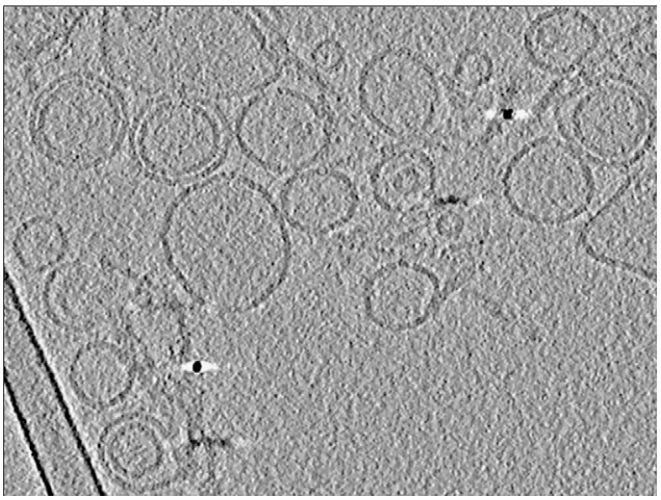
[†]The averages were weighted by the number of liposomes counted, with each dataset in three groups. [‡]R is the ratio of pointed to smooth liposomes.



Movie S1. Cryotomogram of liposomes (~100 nm) with short β_2m amyloid fibrils. The liposomes are deformed into elongated and pointed shapes at sites of contact with the fibrils. Tiny vesicles (15–25 nm) can be seen adjacent to the fibrils. The tomogram was collected at a nominal underfocus of 4 μm to give high contrast and does not resolve the lipid bilayer. The tomogram was denoised by nonlinear anisotropic diffusion as implemented in IMOD (1, 2).

Movie S1

1. Kremer JR, Mastronarde DN, McIntosh JR (1996) Computer visualization of three-dimensional image data using IMOD. *J Struct Biol* 116(1):71–76.
2. Frangakis AS, Hegerl R (2001) Noise reduction in electron tomographic reconstructions using nonlinear anisotropic diffusion. *J Struct Biol* 135(3):239–250.



Movie S2. Cryotomogram of liposomes and amyloid fibrils as above, taken closer to focus. This volume contains several examples of liposomes distorted into points at the sites of contact with fibrils. This tomogram was collected at a nominal underfocus value of 3 μm to resolve the lipid bilayer at the expense of contrast and was denoised as above (1, 2).

Movie S2

1. Kremer JR, Mastronarde DN, McIntosh JR (1996) Computer visualization of three-dimensional image data using IMOD. *J Struct Biol* 116(1):71–76.
2. Frangakis AS, Hegerl R (2001) Noise reduction in electron tomographic reconstructions using nonlinear anisotropic diffusion. *J Struct Biol* 135(3):239–250.